Remarks

Reconsideration of this Application is respectfully requested.

Claims 1-3, 5, 6, 10-13, 35-37, 39-47 and 49 are pending in the application, with claims 1 and 39 being the independent claims.

Based on the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

I. Objection to the Specification

The disclosure was objected to because, according to the Examiner, the status of the U.S. patent applications listed on pages 14 and 20-21 is missing. (*See* Paper No. 32, page 2.) Applicants respectfully request that this ground of objection be held in abeyance until the remaining issues in this application are resolved.

II. Claim Objections

Claims 36 and 37 were objected to as being dependent upon a rejected base claim (claim 1). (*See* Paper No. 32, page 15.) As discussed below, Applicants respectfully traverse the rejection of claim 1. Accordingly, Applicants request that the objection to claims 36 and 37 as being dependent upon a rejected base claim be withdrawn.

III. Claim Rejections Under 35 U.S.C. § 112, First Paragraph

A. Written Description

Claims 1, 2, 3, 5, 6, 10-13 and 35 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. (*See* Paper No. 32, page 3.) The basis for this rejection is the Examiner's assertion that "[t]he specification does not provide sufficient description of a genus of DNA molecules with 90% homology to SEQ ID NO: 1 that codes for a protein that has an activity of AD7c-NTP when over-expressed in neuronal cells." (Paper No. 32, page 4.) Applicants respectfully traverse this rejection for the reasons set forth in Applicants' Amendment and Reply filed on July 7, 2003.

A person of ordinary skill in the art would have recognized that Applicants, at the time the application was filed, were in possession of the invention insofar as it encompasses DNA constructs which comprise the DNA molecule of SEQ ID NO: 1 or a DNA molecule which is at least 90% homologous thereto, wherein said DNA molecule is under control of a heterologous neuro-specific promoter, and wherein said DNA molecule codes for a protein that has an activity of AD7c-NTP when over-expressed in neuronal cells.

First, the DNA molecules of the claims are not defined *solely* in terms of their function. As specified in claim 1, the DNA molecules are at least 90% homologous to SEQ ID NO:1 and are under the control of a heterologous neuro-specific promoter. Thus, the claims include a structural definition of the DNA constructs.

Second, procedures for isolating nucleic acid molecules that are at least 90% homologous to SEQ ID NO:1 are described in the specification and were well-known in the art. (*See, e.g.*, Specification at page 19, lines 3-15.) Moreover, assays are described in the specification for determining whether a DNA molecule encodes a protein having an activity of AD7c-NTP when over-expressed in neuronal cells. (*See* Specification at page 20, line 1, through page 21, line 2.) The specification also provides a working example that describes and illustrates the neuronal abnormalities that are caused by over-expressing AD7c-NTP in neuronal cells. (*See* Specification at page 46, lines 1-26 and Figs. 6A-6G.)

The detail provided in the specification for obtaining DNA molecules that are at least 90% homologous to SEQ ID NO: 1 and for determining whether they encode proteins having an activity of AD7c-NTP when overexpressed in neuronal cells would indicate to persons of ordinary skill in the art that Applicants were in possession of DNA molecules having a nucleotide sequence that is at least 90% identical to SEQ ID NO: 1.

The USPTO's "Synopsis of Application of Written Description Guidelines" and the Federal Circuit's current interpretation and application of 35 U.S.C. § 112, first paragraph, support the conclusion that the present invention is more than adequately described. (*See* Applicants' remarks set forth in the Amendment and Reply filed on July 9, 2002, pages 10-13.) Applicants therefore respectfully request that the written description rejection of claims 1, 2, 3, 5, 6, 10-13 and 35 be reconsidered and withdrawn.

B. Enablement

Claims 1, 2, 3, 5, 6, 10-13, 35 and 44-47 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the

specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. (*See* Paper No. 32, page 6.) Applicants respectfully traverse this rejection.

1. DNA Constructs and Transformed Host Cells

The rejection of claims 1-3, 5, 6 and 35, directed to DNA constructs and host cells transformed with the DNA constructs, is based on three general assertions. First, the Examiner stated that the specification "does not disclose which nucleotides of the claimed DNA molecule [are] considered essential for one skilled in the art to make a representative number of DNA molecules with 90% homology to SEQ ID NO: 1." (Paper No. 32, page 7.) Second, the Examiner asserted that "the specification does not provide sufficient guidance and/or factual evidence for one skilled in the art to determine without an undue amount of experimentation . . . if the nucleic acid sequence with at least 90 percent homology to SEQ ID NO: 1, would exhibit the same biological function of SEQ ID NO: 1." (Paper No. 32, pages 7-8.) Third, the Examiner stated that "the relationship between a sequence of a peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable." (Paper No. 32, page 8.) Applicants respectfully submit that the foregoing reasons do not demonstrate that it would have required undue experimentation to make and use the claimed DNA constructs and transformed host cells.

In order to make and use the claimed DNA constructs and transformed host cells, a person of ordinary skill in the art would not need to know which nucleotides of SEQ ID NO:1 are "considered essential." Nor would a skilled artisan need to be able to predict protein activity from nucleotide sequence. Moreover, the specification provides ample

guidance for determining whether a DNA molecule that is at least 90% homologous to SEQ ID NO:1 encodes a protein that has an activity of AD7c-NTP when over-expressed in neuronal cells.

At the time the present invention was made, persons of ordinary skill in the art could have easily obtained DNA molecules for use with the present invention by: (1) obtaining DNA molecules that are at least 90% homologous to SEQ ID NO:1, and (2) assaying the corresponding proteins for an activity of AD7c-NTP when over-expressed in neuronal cells. One of ordinary skill in the art would have been able to obtain DNA molecules that are at least 90% homologous to SEQ ID NO:1 using only routine methods in the art. (*See, e.g.*, specification at page 19, lines 3-15.) Such methods do not require knowledge of "essential nucleotides," and they do not require the ability to predict a protein's function from its primary structure.

After obtaining a DNA molecule that is at least 90% homologous to SEQ ID NO:1, it would have required no more than routine experimentation to assay the corresponding proteins for an activity of AD7c-NTP when over-expressed in neuronal cells. Contrary to the Examiner's assertion, the specification clearly indicates how to determine whether a given nucleic acid molecule encodes a protein having AD7c-NTP activity.

The specification describes various methods for determining if a nucleic acid molecule encodes a protein with AD7c-NTP activity. For example, transgenic animals can be made that over-express the protein coded by the nucleic acid molecule, and, once obtained, the transgenic animals may be analyzed for evidence of neuronal or neuritic abnormalities associated with Alzheimer's disease, neuroectodermal tumors, malignant astrocytomas or glioblastomas. (*See* specification at page 20, lines 1-29.) Additionally, *in*

vitro methods can be used which involve the overexpression of the protein coded by the nucleic acid molecule in neuronal cells and the subsequent analysis for cellular characteristics of Alzheimer's disease, including apoptosis and neuritic sprouting. (*See* specification at page 46, lines 4-26.) These methods would have enabled a person of ordinary skill in the art to ascertain whether a DNA molecule that is at least 90% homologous to SEQ ID NO:1 has an activity of AD7c-NTP.

Since a person of ordinary skill in the art, based on the present specification, would have easily been able to obtain DNA molecules that are at least 90% homologous to SEQ ID NO:1 and assay the corresponding proteins for an activity of AD7c-NTP when over-expressed in neuronal cells, it cannot be concluded that obtaining DNA molecules for use with the present invention would have involved undue experimentation.

2. Method Claims

Claims 10-13 and 44-47 are directed to screening methods comprising: (a) contacting a candidate drug with the host cell of claim 5 or 42, and (b) detecting at least one of the following: (i) the suppression or prevention of expression of the protein coded for by the DNA construct of said host cell; (ii) the increased degradation of the protein coded for by the DNA construct of said host cell; or (iii) the reduction of frequency of at least one of neuritic sprouting, nerve cell death, degenerating neurons, neurofibrillary tangles, or irregular swollen neurites and axons in said host cell, wherein said host cell is a neuronal cell; due to the drug candidate compared to a control cell line which has not contacted the candidate drug.

The enablement rejection of claims 10-13 and 44-47 is based on three general assertions. First, the Examiner asserted that "[t]he specification does not teach how to distinguish true negatives from false negative[s] or true positives from false positives using the method contemplated in the claimed methods." (Paper No. 32, page 9.) This assertion is based on the notion that, since the DNA molecules used in the practice of the methods are under the control of a heterologous promoter, "[t]he suppression or prevention of expression of the protein coded by the DNA construct in b(i) would reflect interaction with the control sequence and result in false positives/false negatives." (Paper No. 32, page 9.) The second assertion upon which the rejection of the method claims is based is that "the specification does not teach how to distinguish an increase in degradation of the protein coded for by the DNA construct from a decrease [in] expression of the protein coded for by the DNA construct." (Paper No. 32, page 9.) The third assertion in support of the rejection is based on the supposed inability of a skilled artisan to "determine if detection of one of the following from step (b)(i)-(iii) is caused by the drug interacting with the non-coding sequence (e.g., promoter); with the AD7c-NTP cDNA, or independently with another gene product in the cultured cells." (Paper No. 32, pages 9-10.) As discussed below, these assertions do not support a *prima facie* case of lack of enablement.

(a) Identifying "False Negatives" and "False Positives"

The first assertion in support of the enablement rejection concerns the ability of one skilled in the art to identify "false negatives" and "false positives" in the context of (b)(i) of the method claims. The Examiner has apparently assumed that a drug that suppresses or prevents protein expression by interacting with the heterologous neuro-specific promoter

would be a "false positive." This is not the case. As noted in Applicants' previous response, a candidate drug could suppress or prevent the expression of the protein coded for by the DNA construct through mechanisms other than interaction with the promoter. For instance, the drug might stimulate degradation of the mRNA, reduce the stability of the mRNA, or interfere with translation of the mRNA. Drugs that exert such effects could have easily been identified by persons of ordinary skill in the art and would not be regarded as "false positives."

Moreover, Applicants emphasize that the claims are directed to *in vitro* methods for screening a *candidate* drug that is *potentially useful* for the treatment of prevention of Alzheimer's disease, neuroectodermal tumors, malignant astrocytomas, or glioblastomas. In other words, the present claims provide, *inter alia*, an *initial screen* for drugs that are *potentially useful* for the treatment or prevention of Alzheimer's disease and related disorders. The claims do not require confirming whether a candidate drug is clinically effective to treat or prevent Alzheimer's disease. A drug that suppresses or prevents expression of the protein coded for by the DNA construct of the host cell, even if it does so by interacting with the heterologous neuro-specific promoter, would be a "candidate drug that is potentially useful for the treatment of prevention of Alzheimer's disease, neuroectodermal tumors, malignant astrocytomas, or glioblastomas."

(b) Distinguishing an Increase in Protein Degradation from a Decrease in Protein Expression

The second assertion to support the enablement rejection concerns the ability of one skilled in the art to distinguish an increase in protein degradation from a decrease in protein expression. There are numerous methods that were well known in the art at the time of the

invention that could have been used to distinguish (i) the suppression or prevention of expression of the protein coded for by the DNA construct of the host cell, from (ii) the increased degradation of the protein coded for by the DNA construct of the host cell. For example, a Northern blot could be used to assess levels of mRNA in the host cells after being contacted with the candidate drug. A Western blot (or other immunoassay) could be used to assess protein levels. A decrease in protein levels without a decrease in mRNA levels would indicate that the drug increased the degradation of the protein coded for by the DNA construct. A decrease in mRNA levels would indicate the suppression of expression of the protein coded for by the DNA construct. Persons of ordinary skill in the art would have known how to apply such basic techniques to the practice of the claimed methods.

The Examiner dismissed the above argument, stating that "[t]he specification does not contemplate using any method to distinguish between (i) and (ii)." (Paper No. 32, pages 13-14.) The Examiner is reminded that a specification need not supply information that is well known in the art in order to satisfy the enablement requirement. *See Genentech, Inc. v. Novo Nordisk*, 108 F.3d 1361, 1366, 42 USPQ2d 1001, 1005 (Fed. Cir. 1997); *See also Hybritech v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986) ("a patent need not teach, and preferably omits, what is well known in the art.") Thus, a person of ordinary skill in the art would not have to be taught how to distinguish between (i) and (ii) because methods to do so were well known in the art.

It was noted in Applicants' previous response that Northern and Western analyses for AD7c-NTP are exemplified in the specification at page 41, lines 1-28 (Example 5, Northern analysis), and at page 44, line 10 through page 45, line 15 (Example 7: Western analysis). In reply, the Examiner stated that:

> the examples (pages 41-45) do not use a vector comprising a heterologous neuro-specific promoter operably linked to a nucleic acid encoding AD7c-NTP. In addition, the specification does not teach one skilled in the art how to reasonably extrapolate from using a nucleic acid encoding AD7c-NTP not under control of a heterologous promoter or using AD7c-NTP for studying *in vitro* expression to distinguishing an increase in degradation of the protein coded for by the DNA construct from a decrease [in] expression of the protein coded for by the DNA construct in the claimed methods.

(Paper No. 32, page 14.) Thus, it appears to be the Examiner's position that, simply because the Examples in the specification (showing Western and Northern analyses) were not performed in the context of distinguishing an increase in protein degradation from a decrease in protein expression, the Examples do not support the enablement of the present method claims. Applicants disagree with this reasoning.

The claimed methods are fully enabled *even in absence of the Examples*. Persons of ordinary skill in the art would have known how to distinguish between the suppression or prevention of expression of a protein and the increased degradation of a protein even without the added guidance provided by Examples 5 and 7. Therefore, the observation that Examples 5 and 7 were performed in a context other than that of the claimed methods does not support the rejection.

A review of the scientific literature reveals that techniques for distinguishing protein degradation from transcriptional-level regulation were well known in the art. For instance, in Hwong *et al.*, *J. Biol. Chem. 268*:18982-18986 (1993) (copy submitted herewith as Exhibit 1), it is shown that the amount of topoisomerase I protein in phytohemagglutinin (PHA)-stimulated human T lymphocytes was regulated by protein degradation. This conclusion was made by comparing topoisomerase I mRNA levels (determined by

measuring incorporation of radiolabeled thymidine and by Northern analysis (*see* Fig. 3)) to topoismerase I protein levels (determined by Western blot (*see* Fig. 4.)). Although both mRNA and protein levels increased following PHA stimulation, the degree of increase in protein levels was *less than* the degree of increase in mRNA levels. (*See* Hwong *et al.*, paragraph bridging pages 18984-18985.) By measuring [^{35}S] methionine incorporation in the presence of PHA (*see* Fig. 5.), it was confirmed that the discrepancy between mRNA and protein levels was due to degradation of topoisomerase I protein. (*See* Hwong *et al.*, page 18985, paragraph bridging left and right columns.)

Another example is found in Eguchi *et al.*, *Cancer Res.*, *63*:4739-4746 (2003) (copy submitted herewith as Exhibit 2). In Eguchi *et al.*, it was found that addition of *Helicobacter pylori* to AGS human grastric epithelial cells caused a reduction in p27 protein (as determined by Western blot). (*See* Eguchi *et al.*, paragraph bridging pages 4740 and 4741.) The levels of p27 mRNA (as determined by Northern blot), however, were not altered by *H. pylori* treatment. (*See* Eguchi *et al.*, page 4741, left column.) By analyzing metabolically radiolabeled p27, it was confirmed that "the down-regulation of p27 by *H. pylori* is due to increased p27 protein degradation." (*See id.*)

Although Eguchi *et al.* was published in 2003, the general methods used in this reference (*i.e.*, Northern blot, Western blot, and pulse-labeling of proteins) are the same as those used by Hwong *et al.* (published in 1993). Thus, the methodology used by Eguchi *et al.*, would have been known and available to persons of ordinary skill in the art well before the effective filing date of the present application. The techniques used by Hwong *et al.* and Eguchi *et al.* could have been applied by persons of ordinary skill in the art in the context of the present claims to determine if the effect of a candidate drug was due to (i) the

suppression or prevention of expression of the protein coded for by the DNA construct, or (ii) an increase in degradation of the protein. Therefore, destinguishing (i) from (ii) would not have involved anything more than the application of routine techniques.

(c) Mechanism of Action of the Candidate Drug

The third assertion put forth to support the enablement rejection is that:

> [t]he specification does not provide sufficient guidance or factual evidence for one skilled in the art to determine if detection of one of the following from step (b)(i)-(iii) is caused by the drug interacting with the non-coding sequence (e.g., promoter); with the AD7c-NTP cDNA, or independently with another gene product in the cultured cells.

(Paper No. 32, pages 9-10.) In order to practice the claimed methods, however, it is unnecessary for one of ordinary skill in the art to determine the mechanism by which the drug causes at least one of (i), (ii), or (iii), as recited in the claims. As mentioned above, the claimed methods provide an *initial screen* for drugs that are *potentially useful* for the treatment or prevention of Alzheimer's disease or related disorders. Even if the candidate drug causes one of (i), (ii) or (iii) by an indirect mechanism, the candidate drug is nonetheless a drug that is *potentially* useful for the treatment or prevention of Alzheimer's disease, neuroectodermal tumors, malignant astrocytomas, or glioblastomas.

3. Summary

A person of ordinary skill in the art would have been able to make and use the DNA constructs encompassed by claims 1-3, 5, 6 and 35, and would have been able to practice the full scope of the methods encompassed by claims 10-13 and 44-47, without undue experimentation. The Examiner has not presented any specific evidence or sound scientific

reasoning to indicate that it would have required more than routine experimentation to make, use and/or practice the subject matter of the claims. Therefore, the claims are fully enabled and a *prima facie* case of non-enablement has not been established. Accordingly, Applicants respectfully request that the enablement rejection of claims 1, 2, 3, 5, 6, 10-13, 35, and 44-47, be reconsidered and withdrawn.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Frank R. Cottingham

Frank R. Cottingham
Attorney for Applicants
Registration No. 50,437

Date: DEC. 15, 2003

1100 New York Avenue, N.W.
Washington, D.C. 20005-3934
(202) 371-2600